

Effects of different sufentanil target concentrations on the MACBAR of sevoflurane in patients with carbon dioxide pneumoperitoneum stimulus

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Abstract

Background: This study aims to observe the effects of different target controlled plasma sufentanil concentrations on the minimum alveolar concentration (MAC) of sevoflurane for blocking adrenergic response (BAR) in patients undergoing laparoscopic cholecystectomy with carbon dioxide pneumoperitoneum stimulation.

Methods: Eighty-five patients undergoing laparoscopic cholecystectomy, aged 30-65 years, with American Society of Anesthesiologists physical status I-II , were enrolled in this study. All the patients were randomly divided into 5 groups (S_0, S_1, S_2, S_3, S_4) with different sufentanil plasma target concentration (0.0, 0.1, 0.3, 0.5, 0.7 ng ml^{-1}). Anesthesia was induced by inhalation of 8% sevoflurane in 100% oxygen, and 0.6 mg kg^{-1} of rocuronium was intravenously injected to facilitate the insertion of a laryngeal mask airway. The end-tidal sevoflurane concentration and sufentanil plasma target concentration were adjusted according to respective preset value in each group. The hemodynamic response to pneumoperitoneum stimulus was observed after the end-tidal sevoflurane concentration had been maintained stable at least for 15 min. The MAC_{BAR} of sevoflurane was measured by a sequential method. Meanwhile, epinephrine (E) and norepinephrine (NE) concentrations in the blood were also determined before and after pneumoperitoneum stimulus in each group.

Results: When the method of independent paired reversals was used, the MAC_{BAR} of sevoflurane in groups S_0, S_1, S_2, S_3, S_4 was 5.333% (confidence interval [CI] 95%: 5.197-5.469%), 4.533% (95% CI: 4.451-4.616%), 2.861% (95% CI: 2.752-2.981%), 2.233% (95% CI: 2.142-2.324%) and 2.139% (95% CI: 2.057-2.219%), respectively. Meanwhile, when the isotonic regression analysis was used, the MAC_{BAR} of sevoflurane in groups S_0, S_1, S_2, S_3, S_4 was 5.329% (95% CI: 5.321-5.343%), 4.557% (95% CI: 4.552-4.568%), 2.900% (95% CI: 2.894-2.911%), 2.216% (95% CI: 2.173-2.223%) and 2.171% (95% CI: 2.165-2.183%), respectively. The MAC_{BAR} was not significantly different between groups S_3 and S_4 when using 0.5 and 0.7 ng ml^{-1} of sufentanil plasma target concentrations. No significant difference was found in the change of E or NE concentration between before and after pneumoperitoneum stimulation in each group.

Conclusions: The MAC_{BAR} of sevoflurane can be decreased with increasing sufentanil plasma target concentrations. A ceiling effect of the decrease occurred at a sufentanil plasma target concentration of 0.5 ng ml^{-1} . When the sympathetic adrenergic response was inhibited in half of the patients to pneumoperitoneum stimulation in each group, the changes of E and NE concentrations showed no significant differences.

Trial registration: The study was registered at <http://www.chictr.org.cn> (ChiCTR1800015819, 23, April, 2018).

Background

With the development of minimally invasive technique, laparoscopic surgery under inhalation anaesthesia has become increasingly popular in general surgery^[1,2,3].

However, inhalation anaesthetic used alone to provide all the necessary components of general anesthesia under laparoscopic surgery may increase the risk of cardiovascular inhibition and inhaled anaesthetic toxicity^[4,5,6]. Many other agents have been used to decrease the minimal alveolar concentration (MAC) of inhalation anaesthetic^[7,12,8]. Sufentanil, as an adjuvant, offers numerous advantages, including reduced incidence of nausea and vomiting compared with the fentanyl^[9], reduced opioid-induced hyperalgesia compared with the remifentanyl^[10], maintenance of stable hemodynamics, excellent analgesic effect. The MAC of sevoflurane for blocking the adrenergic response (BAR) combined with different sufentanil plasma target concentrations under laparoscopic pneumoperitoneum stimulus has not been reported. Therefore, our primary aim of this study is to observe the MACBAR of sevoflurane combined with different sufentanil plasma target concentrations in patients under carbon dioxide pneumoperitoneum stimulation. A secondary aim is to explore the concentrations of epinephrine and norepinephrine in the blood when the adrenergic response was inhibited in half of the patients

Methods

Study design

The study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College, Nanchong, China (Approved No. 2017/043). Written informed consents were obtained from all participants. All experiment procedures (consisted of invasive manipulation) and data collection were conducted with prior informed consents. This study adhered to the applicable CONSORT guidelines and was registered with the Chinese Clinical Trials Registry at <http://www.chictr.org.cn> (ChiCTR1800015819, principal investigator: Yanxia Guo, date of registration: April 23, 2018) .

The research was conducted between May 2018 and March 2019. Eighty five patients were American Society of Anesthesiologists (ASA) physical status I-II, aged between 30 and 65 years, and randomly assigned to five groups (S0, S1, S2, S3, S4) according to computer generated randomization. Patients in the five groups were anaesthetized by inhalation of sevoflurane and intravenous infusion of sufentanil with different plasma target concentrations (0.0, 0.1, 0.3, 0.5, 0.7 ng ml⁻¹), respectively.

Exclusion criteria included patients with a history of cardiovascular, lung, kidney or brain disease; long-term drug and alcohol abuse; recent taking drugs known to affect the sympathetic adrenergic and cardiovascular systems; body mass index (BMI) ≥ 30 kg m⁻². Withdrawal criteria included the patients with mean arterial pressure (MAP) <50 mmHg or heart rate (HR) < 50 bpm at any time during experimental observation; failing to the creation of carbon dioxide pneumoperitoneum for the first time or asking for adjustment of the pneumoperitoneal pressure above or below the preset value.

Anaesthesia administration

Induction

All patients were fasted at least for 8 h before surgery and without any preoperative medication. Before induction of anaesthesia, patient's MAP, HR, electrocardiogram, pulse oxygen saturation were routinely monitored with a PM-9000 express monitor (Mindray Medical International Limited, Shenzhen, China). Simultaneously, a peripheral intravenous catheter was inserted for infusion of Ringer's solution with a rate of $10 \text{ ml kg}^{-1} \text{ h}^{-1}$. An arterial catheter was inserted into the left radial artery for

monitoring patient's invasive arterial blood pressure and collecting blood samples. Anaesthesia was induced by inhalation of 8% sevoflurane with 100% oxygen until patients lost their consciousness, and 0.6 mg kg^{-1} of rocuronium was intravenously injected to facilitate laryngeal mask airway (Tuoren medical equipment group co. LTD, Henan, China) insertion. Then mechanical ventilation was begun using 100% oxygen with a tidal volume of $6 \text{ to } 8 \text{ ml kg}^{-1}$ in each group. A normal end tidal carbon dioxide (CO₂) tension (35 to 45 mmHg) was obtained by adjusting the respiratory frequency at 12 to 16 breaths min^{-1} . The end-tidal sevoflurane concentration and CO₂ partial pressure were monitored continuously using the above mentioned monitor.

Depth of anaesthesia was monitored by the bispectral index (BIS) (Canwell Medical International Limited, Zhejiang, China) installed before induction.

Measurement of MAC_{BAR}

After laryngeal mask airway insertion, sufentanil was administered by target-controlled infusion with Bovil pharmacokinetic model using a micro pump (TCI-I, ver 4.0, Guangxi VERYARK Technology Co., Ltd), and the plasma target concentration of sufentanil was 0.0, 0.1, 0.3, 0.5, 0.7 ng ml^{-1} in groups S0, S1, S2, S3, S4, respectively. Simultaneously, the inhaled sevoflurane concentration was adjusted to obtain a stable preset end-tidal value according to our pilot study. In order to avoid a potential risk of intraoperative awareness, a higher initial end-tidal sevoflurane concentration was tested in the pilot study. Eventually, the first patient in S0, S1, S2, S3 and S4 group receiving a start end-tidal sevoflurane preset concentration of 5.0%, 4.6%, 3.0%, 2.3% and 2.0% which was measured to be close to the MAC_{BAR}, respectively. An up-and-down sequential-allocation method was applied to determine the MAC_{BAR} of sevoflurane in each group as described in our previous studies^[11,12].

The CO₂ pneumoperitoneum was created when the preset end-tidal sevoflurane concentration had been maintained stable at least 15 min. The creation of pneumoperitoneum was initiated using a Veress needle with CO₂ to 13 mmHg at umbilicus and the insufflation flow rate was set at 3L/min. Then using a 10-mm trocar replaced the Veress needle. Another 10-mm trocar and 5-mm trocar were installed through subxiphoid port and a port in the right subcostal area of the midclavicular line, respectively. HR and MAP were determined before induction, 3 and 1 min before O₂ pneumoperitoneum, 1 and 3 min after three trocars were installed. A positive or negative sympathetic adrenergic response to haemodynamic

parameters (HR or MAP) was observed during the creation of CO₂ pneumoperitoneum. The mean value of the MAP or HR measured 3 and 1 min before pneumoperitoneum stimulation was defined as its pre pneumoperitoneum value, and the mean value of HR or MAP measured 1 and 3 min after three trocars were installed was defined as the post pneumoperitoneum value. If the response was positive (an increase of patient's HR or MAP over 20% of its pre pneumoperitoneum value), the subsequent tested patient's end-tidal sevoflurane concentration would be increased by 0.2%, in contrast, If the response was negative (an increase of HR and MAP less than 20% of its pre pneumoperitoneum value), the subsequent tested patient's end-tidal sevoflurane concentration would be decreased by 0.2%. Patients with bradycardia (HR<50bpm) or hypotension (MAP <50mmHg) at any time during experimental observation administered vascular active drugs such as atropine, ephedrine, would be withdrawn from the study, and the same concentration of sevoflurane was repeated in the following case. The study was continued until six crossing points of a negative versus positive response in the pre-and the next patient had occurred. The investigator responsible for recording the response of the patients to CO₂ pneumoperitoneum was blinded to the plasma target controlled sufentanil concentrations and end-tidal sevoflurane concentration used in all the 5 groups. The MACBAR of sevoflurane in each group was calculated as the mean value of the end-tidal sevoflurane concentrations corresponding to the six crossing points.

After the above test was completed, the target controlled infusion of sufentanil was stopped in each group. The patients in group S0 received an i.v. bolus of 0.3 µg kg⁻¹ sufentanil. Furthermore, the inspired concentration of sevoflurane was adjusted to maintain the end-tidal concentrations at 1.4-1.7 MAC for maintaining the BIS value between 40 and 60. MAP was maintained between 60 and 85 mmHg intraoperatively. If the MAP increased by more than 20% compared with its preoperative value, a bolus of 10 µg sufentanil would be administered. After removed laryngeal mask airway, patients were transported to post- anaesthesia care unit (PACU). In the PACU all patients were asked about whether there was an intraoperative awareness or not.

Analysis of blood samples

Arterial blood samples were collected 3 min before and after CO₂ pneumoperitoneum with sodium-heparin-containing tubes. Soon after, the plasma was separated and kept frozen at -70 °C in a refrigerator until analysis. The method used to measure the concentrations of E and NE in the current investigation had been described previously^[11].

Statistical analysis

Statistical analysis was performed using SPSS 23.0 software. The MACBAR was estimated from the up-and-down sequences using the method of independent paired reversals, which enabled MACBAR with 95% CIs to be derived^[13]. The sequences were also subjected to isotonic regression analyses. To compare the MACBAR from different groups more precisely, the 83% CIs were estimated using the isotonic regression analysis. The delta HR, delta MAP, delta E, delta NE value were calculated as the differences between their average values measured 1 and 3 min after CO₂ pneumoperitoneum and before CO₂

pneumoperitoneum, respectively. The data are presented as mean (SDs or 95%CI). The preoperative data, including gender and ASA class were compared with χ^2 test. The preoperative data (age, BMI), the intraoperative data, the postoperative data, the MACBARS, the concentrations of E and NE, delta E, delta NE, MAP, delta MAP, HR, delta HR were compared among the 5 groups using one-way analysis of variance (ANOVA). P value <0.05 was considered as statistical significance.

Results

A total of 85 patients were recruited in this study. One case in group S0 and one case in group S3 both with MAP <50 mmHg were excluded from the study. Two cases with HR <50 bpm in group S4 were excluded from the study. Eventually, to obtain six crossing points, 14, 14, 18, 20 and 15 patients were used in groups S0-S4, respectively (Fig.1), so that 81 patients completed the study. No significant differences were found in the patients' preoperative data, operation time and rocuronium consumed dose among the 5 groups (table 1). No intraoperative awareness was reported in the postoperative follow up.

Table 1 Patients characteristics and Intraoperative and Postoperative data.

Parameter	Group S ₀	Group S ₁	Group S ₂	Group S ₃	Group S ₄
Preoperative data					
Gender (n, M/F)	6/8	6/8	6/12	10/10	7/8
ASA class (□/□)	7/7	6/8	10/8	10/10	8/7
Age (yr)	41 (8)	38 (9)	37 (10)	41 (11)	39 (9)
Body weight (kg)	68.3 (9.8)	65.7 (8.4)	67.2 (7.9)	66.2(8.5)	67.3 (9.2)
BMI (kg m ⁻²)	23.1 (2.2)	23.4 (2.3)	23.1 (2.7)	23.6 (1.9)	24.0 (2.3)
MAP (mmHg)	92.8 (9.6)	89.8 (6.9)	91.2 (6.7)	89.2 (8.2)	89.9 (9.6)
HR (bpm)	82 (10)	77 (12)	82 (10)	83 (9)	78 (12)
Intraoperative data					
Operation time (min)	62.3 (7.9)	59.6 (8.1)	60.7 (8.9)	56.5 (9.2)	58.9 (5.0)
Total sufentanil consumed dose (µg)	31.4 (5.6)	29.8 (3.9)	30.3 (4.5)	44.6 (5.8)*	61.4 (4.8)* [□]
Rocuronium consumed dose (mg)	35.0 (5.0)	37.5 (6.3)	36.7 (4.9)	38.3 (4.6)	38.6 (6.2)
Postoperative data					
Spontaneous breathing recovery time (min)	5.2 (2.1)	4.8 (2.5)	5.0 (1.9)	4.5 (2.8)	10.0 (3.9) [□]
Eye opening time (min)	7.8 (3.1)	8.0 (1.9)	7.5 (1.8)	8.2 (3.3)	16.4 (5.2) [□]
Extubation time (min)	10.2 (1.7)	11.7 (2.3)	10.5(1.7)	11.0 (3.0)	20.2 (3.8) [□]

Data are presented as mean (SD). * $P < 0.05$ vs. the value of group S₀, S₁, S₂, respectively. # $P < 0.05$ vs. the value of S₀, S₁, S₂, S₃, respectively.

The estimates of MACBAR of sevoflurane by the method of independent paired reversals and isotonic regression using the different plasma target concentration of sufentanil in groups S₀-S₄ were showed in table 2. The 83% CIs overlapped in group S₃ and S₄ using the isotonic regression analysis. For both methods, the MACBAR had no significant difference between group S₃ and group S₄ when using 0.5 and 0.7 ng ml⁻¹ of sufentanil plasma target concentrations. The data of HR and delta HR were similar among groups S₂, S₃, and S₄, but significantly lower than the group S₀ and S₁ ($P < 0.05$, Table 3). No significant differences were found in the MAP, delta MAP, epinephrine and norepinephrine concentration, delta epinephrine and norepinephrine concentration among the 5 groups (table 3). The total administered dose of sufentanil in both group S₃ and group S₄ was higher than that in the group S₀, S₁, S₂ ($P < 0.05$, Table

1). The spontaneous breathing recovery time, eye opening time and extubation time in the group S4 were longer than those in the other 4 groups, respectively ($P < 0.05$, Table 1).

Table 2 The MAC_{BAR} of sevoflurane using the method of independent paired reversals and isotonic regression analyses in 5 groups

Group	Target concentration of sufentanil (ng ml ⁻¹)	Empirical mean MAC _{BAR} (95% CI)	Isotonic regression MAC _{BAR} (95% CI), (83% CI)
S ₀	0.0	5.333(5.197-5.469)	5.329(5.321-5.343) (5.324-5.339)
S ₁	0.1	4.533 (4.451-4.616)*	4.557(4.552-4.568) (4.555-4.566)
S ₂	0.3	2.861(2.752-2.981)* [□]	2.900(2.894-2.911) (2.898-2.909)
S ₃	0.5	2.233 (2.142-2.324)* [□] *	2.216(2.173-2.223) (2.177-2.212)
S ₄	0.7	2.139 (2.057-2.219)* [□] *	2.171(2.165-2.183) (2.170-2.180)

The data of MAC_{BAR} were presented as means (95% CI or 83% CI).

* $P < 0.05$ vs. value of group S₀. [□] $P < 0.05$ vs. value of group S₁. * $P < 0.05$ vs. value of group S₂.

Table 3 The comparison of MAP, HR, epinephrine and norepinephrine concentrations before and after pneumoperitoneum stimulus among 5 groups.

MAP (mmHg)					
Before pneumoperitoneum	63 (5)	62 (4)	64 (4)	63 (5)	62 (5)
After pneumoperitoneum	78 (8)	75 (8)	79 (8)	78 (7)	76 (6)
Delta	15 (7)	13 (8)	15 (6)	16 (2)	14 (8)
HR (bpm)					
Before pneumoperitoneum	89 (11)	82 (15)	67 (6)* [□]	61 (5)* [□]	62 (6)* [□]
After pneumoperitoneum	100 (13)	92 (15)	69 (7)* [□]	64 (8)* [□]	66 (6)* [□]
Delta	11 (5)	10 (4)	2 (1)* [□]	3 (1)* [□]	3 (2)* [□]
Epinephrine (ng ml ⁻¹)					
Before pneumoperitoneum	2.85 (0.23)	2.97 (0.19)	2.92 (0.19)	2.82 (0.28)	2.67 (0.18)
After pneumoperitoneum	2.92 (0.25)	3.04 (0.40)	2.91 (0.17)	2.85 (0.29)	2.62 (0.11)
Delta	0.07 (0.04)	0.07 (0.02)	0.03 (0.02)	0.03 (0.01)	-0.04(0.03)
Norepinephrine (ng ml ⁻¹)					
Before pneumoperitoneum	3.23 (0.21)	3.63 (0.23)	2.89 (0.19)	3.18 (0.95)	3.12 (0.74)
After pneumoperitoneum	3.11 (0.33)	3.55 (0.13)	2.81 (0.25)	3.15 (0.65)	3.07 (0.45)
Delta	-0.12(0.07)	-0.08(0.04)	-0.08(0.05)	-0.03(0.02)	-0.05(0.03)

The value of each parameter before pneumoperitoneum was the average value measured 3 and 1 min before CO₂ pneumoperitoneum. The value of each parameter after pneumoperitoneum was the average value measured 3 and 1 min after CO₂ pneumoperitoneum and the delta value of each parameter was the difference between the average value measured 1 and 3 min after CO₂ pneumoperitoneum and before CO₂ pneumoperitoneum value. **P* < 0.05 vs. values of group S₀. [‡]*P* < 0.05 vs. values of group S₁.

Discussion

The results of this study indicate that the reduction of the MACBAR of sevoflurane is dose-dependent. The overlapped 83% CIs in group S3 and S4 using the isotonic regression analysis indicate the MACBAR had no significant difference when using 0.5 and 0.7 ng ml⁻¹ of sufentanil plasma target concentrations. This implicated that the ceiling effect of the decrease of MACBAR of sevoflurane was occurred when sufentanil plasma target concentration increased to > 0.5 ng ml⁻¹ (Table 2). The ceiling effect of sufentanil was similar to the result measured by Brunner and colleagues^[14] at the same plasma target concentration when they evaluated the reduction of soflurane's MAC by sufentanil responding to skin incision. As all know, sufentanil is a μ receptor agonist, which can be saturated when its plasma target concentration beyond a certain level^[15]. Therefore, we speculate that a similar ceiling effect will occur under a similar plasma target concentration of sufentanil no matter what kinds of surgery and stimulus are selected. However, the plasma target concentration of sufentanil (0.18 ng ml⁻¹) for occurring ceiling effect in Shun-Huang and colleague's study^[16] is significantly lower than that of our experiment result. It may be reasonably explained by the concomitant administration of 60% nitrous oxide^[17-18]. Studies

shows nitrous oxide can combine with the μ receptor and decrease the binding sites of sufentanil in humans^[19,20,21,22,23].

In this study, the MACBAR of sevoflurane (5.333%) under laparoscopic pneumoperitoneum stimulation is higher than that measured by Katoh and his colleagues (4.15%) under skin incision^[24]. It indicates that the laparoscopic pneumoperitoneum stimulus is stronger than the skin incision stimulus, so that a higher concentration of sevoflurane is needed to inhibit the stress reaction in laparoscopic surgery, which is consistent with the results of our previous study^[25]. However, the MACBAR of sevoflurane measured in this study is also significantly higher than the value (4.6%) reported in our previous study in gynecologic patients^[12]. Although the same CO₂ pneumoperitoneum stimulus was used, the MACBAR of sevoflurane could be affected by many factors, such as the location of perforation for establishing pneumoperitoneum, the patient's age and sex^[26,27], the methods of measurement^[29-29] and the criterion of judgment for a positive or negative response, et al^[31-31]. Dixon thought that the MACBAR values could be estimated as the mean of four independent crossovers of responses^[28]. Paul and his colleagues thought that the reliability of the Dixon method increased with the number of pairs and six pairs was enough^[29]. An increase of 15% or more from the baseline value of MAP or HR was taken as the criterion of a positive response in many studies^[30,31]. However, in clinic, the fluctuation of MAP or HR within the range of 20% is also acceptable and reasonable. Therefore, in our current study, an increase of 20% or more from pre-pneumoperitoneum stimulation values of MAP or HR was taken as the standard to judge a positive response.

Our results indicated the delta E or NE concentration did not differ among all the 5 groups (Table 3). It implied that when the sympathetic adrenergic response was inhibited in half patients to pneumoperitoneum stimulation in each group, the change of E or NE concentration would be similar, no matter the target controlled sufentanil concentration and the end tidal sevoflurane concentration how to change. Our results also showed patients' HR could be depressed to some degree with the increase of sufentanil plasma target concentration (Table 3). However, the decrease in HR did not result in a decrease of patients' MAP, especially when high concentration of sufentanil was administrated. It implies the safety range of sufentanil is large, which is consistent with the results of Fechner and his colleagues^[32]. Nevertheless, our study showed the use of sufentanil at a large dose results in the delay of anaesthesia recovery (table1). Therefore, the administration of sufentanil with large dose for short surgery such as laparoscopic cholecystectomy is not recommended.

There are several potential limitations to our study. First, we did not measure arterial blood gas during the pneumoperitoneum period. Although the end-expiratory CO₂ partial pressure was maintained in normal range by adjusting the tidal volume and respiratory rate, it was still necessary to measure the actual CO₂ partial pressure to exclude the influence of hypercarbia on sympathetic adrenergic response. Second, we did not measure the actual plasma sufentanil concentration. Although the Bovill pharmacokinetic model for target-controlled infusion has been shown to be safe in Asian people, it is still necessary to measure the actual plasma sufentanil concentration to exclude individual error. Third, we did not perform the

monitoring of muscle relaxation. The level of neuromuscular blockade may influence the relaxation of the abdominal muscles, so as to affect the creation of pneumoperitoneum easily or difficultly and further potentially affect the adrenergic response during CO₂ insufflation.

Conclusions

The MAC_{BAR} of sevoflurane can be decreased with increasing sufentanil plasma target concentrations. A capping effect of the decrease occurred at a sufentanil plasma target concentration of 0.5 ng ml⁻¹. When the sympathetic adrenergic response was inhibited in half patients to pneumoperitoneum stimulation in each group, the changes of E and NE concentrations showed no significant differences.

Abbreviations

MAC_{BAR}: minimum alveolar concentration of sevoflurane for blocking adrenergic response; **E**: epinephrine; **NE**: norepinephrine; **CI**: confidence interval; **BMI**: body mass index; **ASA**: American Society of Anesthesiologists; **CO₂**: Carbon dioxide; **BIS**: Bispectral index; **MAP**: Mean arterial pressure; **HR**: Heart rate; **PACU**: post-anesthesia care unit

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College, Nanchong, China (Approved No. 2017/043). Written informed consents were obtained from all participants. All experiment procedures (consisted of invasive manipulation) and data collection were conducted with prior informed consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no conflicts of interest.

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Authors' contributions

YX G and D W were the co-first authors of this article, conducted the study, collected and analyzed the data and wrote the paper. XL Y was the corresponding authors of this article, helped with the study design and revision of the paper. PP J and J X helped with the clinical anaesthesia management. GY Z helped with the determination of blood samples. All authors read and approved the final manuscript.

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Figures

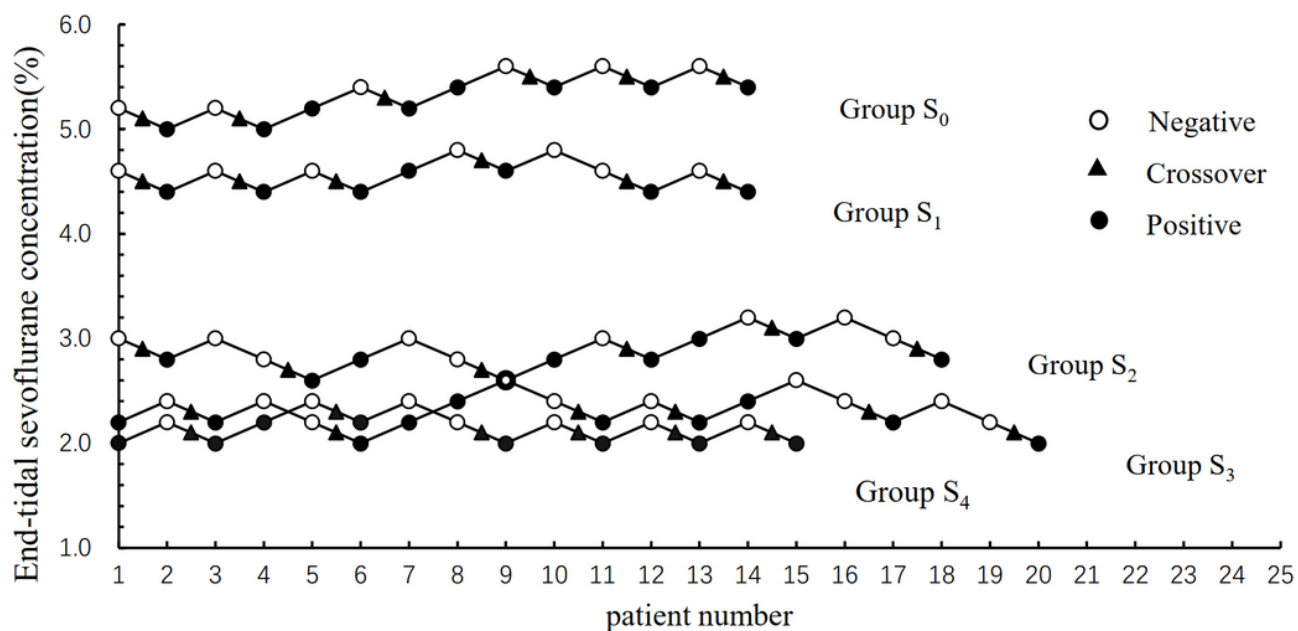


Figure 1

Dixon up-and-down plots for each group. The plasma target concentration of sulfentanyl in groups S₀, S₁, S₂, S₃ and S₄ was 0.0, 0.1, 0.3, 0.5 and 0.7 ng ml⁻¹, respectively. The empty (solid) circle represents the

negative (positive) reaction to hemodynamics parameters, and the triangle indicates the intersection of negative and positive reactions. The ninth patient was given the same concentration of sevoflurane both in group S2 and group S3. To get six crossovers, 14, 14, 18, 20 and 15 patients were needed in groups S0-S4, respectively.

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